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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/350,202	07/08/1999	CARL H. JUNE	36119-125US9	7708

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EXAMINER	
GAMBEL, PHILLIP	
ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 10/16/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/350,202	Applicant(s) JUNE
	Examiner GAMBEL	Art Unit 1644

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☑ Responsive to communication(s) filed on 5/5/03; 8/7/03

2a)☐ This action is **FINAL**. 2b)☑ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☑ Claim(s) _____ is/are pending in the application. 50, 53, 57-58

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected. 50, 53, 57-58

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☑ The translation of the foreign language provisional application has been received.

15)☑ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☑ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4)☐ Interview Summary (PTO-413) Paper No(s). _____.
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other:

PAPER NO. 23

DETAILED ACTION

1. Applicant's amendment, filed 5/503 (Paper No. 20), has been entered.

Applicant's amendment, filed 8/7/03 (Paper No. 22), has been entered
Claims 50, 53 and 57 have been amended.
Claims 1-49, 51-52, 54-56 and 59 are canceled.

Claims 50, 53 and 57-58 are under consideration in the instant application.

2. The text of those sections of Title 35 USC not included in this Action can be found in a prior Action.
This Action will be in response to applicant's amendments, filed 5/503 (Paper No. 20) and filed 8/7/03 (Paper No. 22).
The rejections of record can be found in previous Office Action (Paper No. 19).

3. Formal drawings submitted 5/5/093 comply with 37 CFR 1.84.

4. Upon reconsideration of applicant's arguments, filed 5/5/03 (Paper No. 20), the previous rejection under 35 U.S.C. § 102(e) as being anticipated by Ledbetter et al. (U.S. Patent No. 6,010,902) has been withdrawn as the referenced heteroconjugates or bispecific antibodies comprising antibodies are distinguishable from the claimed agents / antibodies covalently attached to a solid surface.

5. Claims 50, 53 and 57-58 are rejected under 35 U.S.C. § 103 as being unpatentable over Ledbetter et al. (EP0440373; 1449, #A2) in view of Ledbetter et al. (U.S. Patent No. 6,010,902) and Chang (U.S. Patent No. 6,129,916; 1449) essentially for the reasons of record.

Applicant's arguments, filed 5/5/03 (Paper No. 20), have been fully considered but are not found convincing essentially for the reasons of record.

Applicant is reminded that essentially all that is required is that an anti-CD3 antibody and anti-CD28 antibody are covalently attached to the same solid surface in methods to induce ex vivo proliferation of a population of T cells.

Applicant asserts that Ledbetter et al. (EP0440373) teach methods of potentiating the development of CD3-independent cytolytic activity, with antibodies wherein both are soluble or one is immobilized and the other is in soluble form, which is distinguishable from the instant methods wherein both antibodies (e.g. anti-CD3 and anti-CD28) must be immobilized on the same surface.

As pointed out previously, Ledbetter et al. (EP0440373) teach methods of activating T lymphocytes with immobilized anti-CD3 and immobilized anti-CD28 antibodies, including whole antibodies, where the anti-CD3 antibodies are immobilized on the solid supports, including Sepharose beads and the anti-CD28 is cross-linked by a variety of means, including immobilized to plastic surfaces (see entire document, including Contact with CD3 or CD28 Antibody and Crosslinking on page 4 and Claims, e.g. claims 1, 9, 20). Ledbetter et al. provide an Example of culturing for three days (page 6, last paragraph) and teaches preparing cells for adoptive immunotherapy (page 4, Therapy).

Ledbetter et al. (EP0440373) differ from the claimed methods by not exemplifying combining anti-CD28 and anti-CD3 antibodies on the same plate; however it is clear that Ledbetter et al. do teach combining both specificities to stimulate T cells and to immobilize both antibodies on plastic surfaces.

Note that in the section on Crosslinking (page 4), Ledbetter et al. (EP0440373) teach alternative methods off accomplishing activation via anti-CD28 antibodies, including crosslinking by secondary antibodies, aggregating by homoconjugates or aggregating by immobilized antibodies.

Note that Ledbetter et al. (EP0440373) teach that immobilized anti-CD3 antibodies may be added with the anti-CD28 antibodies to the lymphocytes in vitro to achieve induction of cytolytic activity in the lymphocytes (see page 4, paragraph 4, particularly, lines 40-43 and Claims 1, 9 and 20). Also it is noted that product claims recite cytolytic lymphocytes obtainable by a process exposure to both anti-CD28 antibodies and anti-CD3 antibodies, wherein the antibodies are immobilized as well (e.g. claims 49-50, 54).

Therefore, in contrast to applicant's assertions, Ledbetter et al. (EP0440373) is not limited CD3-independent activation of lymphocytes.

Applicant asserts that Ledbetter et al. (EP0440373) do not teach a methods of stimulating a population of T cells to proliferate but that Ledbetter et al. is limited to stimulating cytotoxic activity.

In contrast to applicant's assertions, there is no manipulative difference between the prior art methods and the claimed invention. The induction of cytotoxic lymphocytes involved activation , cytokine production, blast transformation, DNA synthesis and cell proliferation. Costimulation via CD28 leads to effective proliferation of cytotoxic lymphocytes.

Also, it is noted that Ledbetter et al. ('902) do teach stimulating T cells with the combination of antibodies to CD3 and anti-CD28 antibodies (e.g. 9.3) in order stimulate T cell populations and subpopulations and reinfused in patients (e.g. see columns 15-16) (see entire document, including Detailed Description of the Invention and Examples). The Detailed Description of the Invention provides numerous teachings that these cell populations have increased signal transduction, which can be measured by various known assays.

Applicant asserts that Change et al. Does not remedy the deficiencies of the two Ledbetter patents and asserts that there is no teaching or suggestion in Chang that would motivate an ordinary skilled artisan to select antibodies that bind CD3 and antibodies that bind CD28 among the laundry list of antibodies which are taught to be useful for activating T cells in vivo.

Applicant asserts that Chang teaches away from an in vitro method of activating T cells by teaching a major concern with in vitro regimens.

In further support of the teachings of Ledbetter et al. ('902), Chang provides a clear teaching of combining the particular CD3 and CD28 specificities, by teaching the use of microbeads and cross-linking by well-established manner (columns 7-8) in cross-linking anti-CD3 and anti-CD28 antibodies on microbeads to activate T cells in vivo (see entire document, including Summary of the Invention and Detailed Description of the Invention).

Although it is noted that Chang focuses on the in vivo administration of stimulating immunoconjugates; Chang clearly that it was known to stimulate T cells in vitro via immobilized stimuli (see Background of the Invention). Further, both Ledbetter et al. References teach stimulating T cells for adoptive immunotherapy via CD3 and CD28 stimulation.

In contrast to applicant's attempts to draw conclusions about the opposite effects between anti-CD3 antibodies in vivo and in vitro, it is noted that the inhibitory effects of anti-CD3 / OKT3 in vivo are associated with soluble anti-CD3 antibodies, while the stimulatory effects of anti-CD3 / OKT3 has been long established with cross-linked or immobilized anti-CD3 / OKT3. Such differences have been long known and established in the art at the time the invention was made.

Again in response to applicant's assertions concerning monitoring cell proliferation and as noted previously, it was an art known practice to monitor cell proliferation of interest, including cell size and cell markers at the time the invention was made; as such criteria were known parameters of cell activation. Also, it was common practice at the time the invention was made to re-activate and re-stimulate cells to maintain proliferation and expansion of cell populations of interest at the time the invention was made. Here, both Ledbetter et al. references teach methods of preparing cells for adoptive immunotherapy, which required large numbers of cells resulting from multiple stimulation. Therefore, one of ordinary art at the time the invention was made would have expected to monitor the proliferation of said T cells by various parameters and to re-stimulate T cells undergoing expansion to achieve large number of cells of interest. It is noted that applicant has not seasonally traversed this aspect of the rejections of record. Also, it is noted that Ledbetter (U.S. Patent No. 6,010,902) teach various assays and procedures to monitor the cells such as cell sorting, immunofluorescence, cell cycle as well as functional assays (see Detailed Description of the Invention).

One of ordinary skill in the art at the time the invention was made would have been motivated to stimulate T cell activation with both CD3-/CD28-specific antibodies, including covalently linking both stimuli to the same solid phase surface, to increase T cell proliferation and numbers of T cells of interest for various purposes, such as T cell studies and adoptive immunotherapy. One of ordinary skill in the art at the time the invention was made would have been motivated to provide immobilized CD3 and CD28 signaling simultaneously on the same plate as an efficient means to stimulate T cells over extended periods of times to grow T cells of interest, including growing large numbers of T cells for adoptive immunotherapy in the treatment of certain diseases and conditions, as taught by the Ledbetter et al. references. The ordinary artisan was motivated to monitor the activation of T cells by the known practices of monitoring cell size and cell surface markers to measure said T cell activation at the time the invention was made. To achieve large numbers of cells or maintain activated T cells, it was routinely practiced by the ordinary artisan at the time the invention was made to re-stimulate or re-activated T cells with the appropriate stimuli. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary

. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicant's arguments are not found persuasive.

6. Claims 50, 53 and 57-58 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over
copending claims of commonly assigned copending USSN 08/253,964;
copending claims of commonly assigned copending USSN 08/592,711;
copending claims of commonly assigned copending USSN 09/183,055;
copending claims of commonly assigned copending USSN 09/349,915; and
Copending claims of commonly assigned copending USSN 09/553,865.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant and copending claims appear to rely upon the same or nearly the same method steps and ingredients, particularly the use of anti-CD3 and anti-CD28 antibodies to stimulate and expand T cells.

This is a *provisional* obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicant's amendment, filed 5/5/03 (Paper No. 20), notes that a terminal disclaimer may be filed when allowable subject matter is indicated.